REMARKS

Reconsideration of the instant application in view of the above amendments and the following remarks is respectfully requested. Claims 42, 44-46, and 48-79 are currently pending. By the present amendment, claim 42 has been amended to more specifically recite certain aspects of the invention related to the charge ratio of cationic lipid to anionic nucleic acid within the claimed nucleic acid-lipid particles. New claims 80-83, which depend from claim 42, have been added. Claims 69, 70, and 72-75 have been canceled without acquiescence to any rejection. Support for these amendments may be found throughout the specification and claims as originally filed. Therefore, the amendments do not constitute new matter. It should be noted that the above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application.

Rejections Under 35 U.S.C. §§ 102(e) and 103(a)

Claims 42, 44-46, 48-61, 63-77, and 79 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,820,873 (Choi). In addition, claims 42, 44-46, 48-61, 63, 64, 67-77, and 79 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,885,613 (Holland). Claims 62, 75-77, and 79 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Choi. The Examiner points out that the instant claims are directed to compositions of matter, and asserts that both Choi and Holland teach chemical compositions as claimed. Claim 68, which recites the feature that the nucleic acid is double-stranded RNA does not stand rejected under 35 U.S.C. § 102 or § 103.

In the response filed December 14, 2005, Applicants submitted the Declaration of Dr. Ian MacLachlan, which demonstrated that the methods of Choi and Holland, when used in an

attempt to encapsulate plasmid DNA, result in an inoperative plasmid DNA-lipid composition. Since the submission of this declaration, Dr. MacLachlan has conducted similar experiments using oligodeoxynucleotides (ODNs), which indicate that the methods of Choi and Holland are more efficient at producing nucleic acid-lipid compositions comprising ODNs than plasmid DNA. These results are summarized in the attached Declaration of Dr. Ian MacLachlan.

In order to expedite prosecution of the instant application, and without acquiescence to these bases of rejection, Applicants have amended independent claim 42 to recite the feature that the claimed particles have a charge ratio of cationic lipid to anionic nucleic acid within the range of 1:1 to 8:1. In addition, Applicants have added claims 80 and 81, which recite charge ratios of 2:1 to 8:1 and 2:1 to 6:1. Support for this amendment is provided in the instant application. The instant application describes numerous experiments examining the effects of charge ratios ranging from 1:1, 1.5:1, 2:1, 4:1, and 8:1 (*see, e.g.*, Table 3). In addition, the instant application specifically describes several charge ratios, including ratios of about 1:1 to about 12:1 and about 2:1 to about 6:1 (page 24, lines 27-29).

As enunciated in the M.P.E.P. § 2163.05, with respect to numerical range limitations, analysis of whether the range is supported by the application must take into account which ranges one skilled in the art would consider inherently supported by the discussion in the original disclosure. In the decision in *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976), the ranges described in the original specification included a range of "25%- 60%" and specific examples of "36%" and "50%." A corresponding new claim limitation to "at least 35%" did not meet the description requirement because the phrase "at least" had no upper limit and caused the claim to read literally on embodiments outside the "25% to 60%" range, however a limitation to "between 35% and 60%" did meet the description requirement. Applicants submit that this situation is analogous to the present situation, in which the instant application specifically discloses ranges of 1:1 to 12:1 and 2:1 to 6:1, as well as specific examples of 8:1. Clearly, one skilled in the art would consider the claimed range of 1:1 to 8:1 and 2:1 to 8:1 inherently supported by the instant application.

Applicants submit that neither Choi nor Holland teach or suggest nucleic acid-lipid particles having a charge ratio of cationic lipid to anionic nucleic acid of 1:1 to 8:1, 2:1 to

8:1, or 2:1 to 6:1, or the advantages associated with such charge ratios. Thus, neither Choi nor Holland teach each limitation of the instant claims, and neither reference, therefore, anticipates or rendes obvious the instant claims.

As described in the instant application, an important feature of the claimed nucleic acid-lipid particles is the charge ratio between the cationic lipid and anionic nucleic acid present in the particle (*see, e.g.*, page 24, lines 27-29). Indeed, nucleic acid-lipid particle formation and stability is believed to be dependent on cationic lipid binding to anionic nucleic acid (*see, e.g.*, page 70, lines 4-5). In particular, Example 20 describes experiments demonstrating that the charge ratio of cationic lipid to anionic nucleic acid directly affects particle structure, and that this effect is observed in particles composed of different combinations of lipids. For example, nucleic acids present in particles comprising DODAC/ESM at a charge ratio of 4:1 are fully protected by the lipid component (Figure 32). Nucleic acids present in particles comprising DODAC/DOPE are partially protected at a charge ratio of 4:1 but fully protected at a charge ratio of 8:1 (Figure 32). This result suggests that the nucleic acid is partially condensed at the lower charge ratio and fully condensed at the higher ratio.

The instant application further demonstrates that the charge ratio of cationic lipid to anionic nucleic acid present in particles affects their ability to deliver nucleic acids to cells. Example 23 describes experiments demonstrating that the efficiency with which claimed particles are able to transfect cells *in vitro* is related to the charge ratio of cationic lipid to anionic nucleic acid present in the particles. In this experiment, using particles comprising either DODAC/ESM or DODAC/DOPE, a cationic lipid to anionic nucleic acid charge ratio of 3:1 to 4:1 provided the best transfection results. The data obtained for the particles comprising DODAC/ESM is shown in Figure 34.

In addition, Example 25 describes experiments wherein the ability of nucleic acid-lipid particles encapsulating a plasmid encoding for β-galactosidase to transfect CHO cells is compared as a function of cationic lipid to anionic nucleic acid charge ratios. As shown in Figure 39A, significant transfection was achieved at a charge ratio of 1:1, and transfection efficiency increased as the charge ratio increased from 1:1 to 1:4.

These results establish the importance of charge ratio for particle structure and associated function, particularly in the delivery of nucleic acids to cells. In addition, they identify ranges of charge ratio that correlate with transfection of nucleic acids into cells, including the cationic lipid to anionic nucleic acid charge ratio 1:1 to 8:1, within which successful transfection was demonstrated, as well as the narrower ranges of 2:1 to 8:1 and 2:1 to 6:1, which ranges were associated with enhanced *in vitro* transfection results.

As discussed above, neither Choi nor Holland teach or suggest nucleic acid-lipid particles having a charge ratio of cationic lipid to anionic nucleic acid of 1:1 to 8:1, 2:1 to 8:1, or 2:1 to 6:1, or the advantages associated with such charge ratios. Thus, neither Choi nor Holland teach each limitation of the instant claims and cannot, therefore, anticipate or render obvious such claims. It is only the instant application that teaches the specifically claimed charge ratios and associated advantages. In light of the amendments and comments above, Applicants respectfully request that the Examiner reconsider and withdraw these bases of rejection.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 42, 44-46, and 48-79 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. In response to Applicants' remarks submitted on December 14, 2005, the Examiner asserts that the descriptions of various nucleic acid-lipid particles provided in the instant specification are not representative of the claimed genus and, thus, do not adequately describe the claimed genus. The Examiner makes no comment regarding Applicants' assertion that the written description requirement is satisfied by the disclosure of relevant, identifying characteristics, sufficient to show that Applicants were in possession of the claimed genus.

Applicants respectfully traverse this basis of rejection and submit that the instant claims satisfy the written description requirement.

Applicants note that under the Examination Guidelines set forth by the Patent and Trademark Office, the written description requirement for a claimed genus may be satisfied by the description of a representative number of species or the disclosure of relevant, identifying

characteristics, sufficient to show the applicant was in possession of the claimed genus. Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, ¶1, "Written Description" Requirement, 66 Fed. Reg. 1099, at 1106. Applicants submit that the instant application both describes a representative number of claimed nucleic acid-lipid particles, and also describes relevant, identifying characteristics of the claimed particles sufficient to meet the written description requirement.

Applicants maintain their position that the instant specification describes a representative number of claimed species, since it describes at least five different species of claimed particles, each comprising a different cationic lipid, and all of which provide increased encapsulation of nucleic acids, as shown in Figure 41. In addition, Applicants submit that the skilled artisan would immediately recognize that the claimed invention could comprise any of a large variety of cationic lipids, non-cationic lipids, conjugated lipids, and nucleic acids. This is further supported by the results of Example 13, which indicate that three different monovalent cationic lipids behave in similar fashion in the nucleic acid-lipid particles of the present invention.

Applicants also submit that the instant specification discloses sufficient identifying characteristics to support the claimed particles, since it provides in-depth description of both structural and functional characteristics of the claimed particles. As described in the claims and throughout the instant specification, the claimed nucleic acid-lipid particles comprise a cationic lipid, a non-cationic lipid, a conjugated lipid, and a nucleic acid, wherein said nucleic acid is encapsulated in the lipid of said particle and is resistant in aqueous solution to degradation with a nuclease. These recited features serve to sufficiently identify the claimed nucleic acid-lipid particles, and thereby further demonstrate that Applicants had possession of the claimed invention at the time of filing the instant application. Clearly, it is not necessary for Applicants to demonstrate a working example of each species that falls within the claimed genus in order to describe their invention. This is particularly true, since it is not necessarily the specific component, *e.g.*, the particular cationic lipid, selected, but, rather, it is shared characteristics, *e.g.*, its cationic nature, that is important to the claimed invention.

As noted previously, the skilled artisan would appreciate from the teachings of the instant specification that each of the specific lipid or nucleic acid components can vary significantly, while retaining the recited functional properties, since it is the general nature and combination of components that achieves the desired result, as opposed to any one specific species of component. For example, it is understood that cationic lipids are used to neutralize a portion of the negative charge associated with nucleic acid molecules, as described on page 29, lines 8-10. Also, it would be readily understood by one of skill in the art that any of a variety of conjugated lipids would serve to inhibit aggregation, and that any of a variety of different nucleic acid molecules cold be used according to the invention, as described throughout the instant application. Accordingly, the skilled artisan would appreciate that Applicants had possession of the claimed genus, in light of the teachings of the instant specification, which provides numerous specific representative species, as well as description of alternate components suitable for use in the claimed particles.

For the reasons stated above, Applicants submit that the written description requirement is fully satisfied for the instant claims. Applicants have also added new claims 82 and 83, which explicitly recites specific cationic lipids, non-cationic lipids, and conjugated lipids that may be combined in the claimed nucleic acid-lipid particles. Applicants respectfully request that the Examiner reconsider and withdraw this basis of rejection, particularly in light of Applicants' comments that the instant specification provides relevant, identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Claim 78 stands rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description support in the specification for double -stranded RNA.

Applicants respectfully traverse this basis of rejection and submit that support for double-stranded RNA is provided throughout the instant specification as filed. For example, page 13, lines 17-19, specifically indicates that the term "nucleic acid" includes ribonucleotide polymers in either single- or double-stranded form, thereby describing double-stranded RNA. Furthermore, page 32, line 25, specifically recites that "[t]he exogenous nucleic acid is typically dsDNA, ssDNA, ssRNA, dsRNA..."(emphasis added), thereby providing additional and specific

written support for particles comprising dsRNA. Applicants respectfully request that the Examiner reconsider and withdraw this basis of rejection.

Claims 69, 70, and 72-75 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement. The Examiner asserts that the specification, while enabling for *in vitro* transfection of target cells with nucleic acid using lipid formulations particularly described in the examples delineated in the specification, does not reasonably provide enablement for methods of *in vivo* gene delivery and treatment effects provided for the broad genus of compositions claimed.

Applicants traverse this basis of rejection and submit that the instant claims are fully enabled. However, solely to expedite prosecution of the instant claims, and without acquiescence to this basis of rejection, Applicants have canceled these claims without prejudice to their prosecution in a continuing application.

Obviousness-Type Double Patenting

Claims 42, 44-46, 48-68, 76, 77, and 79 stand rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 7, 13, 23, and 29 of U.S. Patent No. 5,976,567. The Examiner asserts that the claimed subject matter of the conflicting claims is not distinct, since both claimed inventions are drawn to compositions comprising nucleic acid-lipid particles of one or more cationic lipids, a conjugated lipid that inhibits aggregation of particles, and which further comprise non-cationic lipids, whereby the nucleic acids are encapsulated in the lipids and are resistant to nuclease degradation and the particles are inhibited from aggregating.

Without acquiescence to this basis of rejection, Applicants submit with this amendment a terminal disclaimer with respect to U.S. Patent No. 5,976,567, thereby overcoming this basis of rejection.

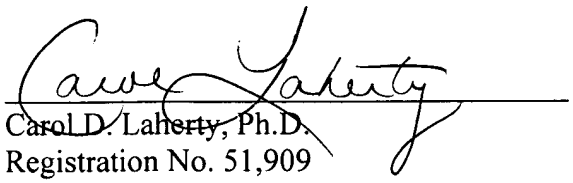
Applicants respectfully request that the Examiner reconsider and withdraw these bases of rejection, in light of the amendments and remarks provided herein.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that all of the claims remaining in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. However, should any issues remain, the Examiner is urged to contact the undersigned at (206) 694-4887.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC



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Enclosures:
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